DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 22 2002

John Seager
Director of Operations
Buffalo Technical Operations
Westwood Squibb Pharmaceuticals, Inc.
100 Forest Avenue
Buffalo, NY 14213

Re: Docket No. 95P-0379/CP 1

Dear Mr. Seager:

This responds to your citizen petition dated November 17, 1995, concerning bioequivalence requirements for ammonium lactate lotions, which are drug products indicated for treatment of xerosis and ichthyosis vulgaris. Your petition requests that the Food and Drug Administration (FDA) modify its advice for establishing the bioequivalence of generic ammonium lactate lotions to conform to methodologies used by Westwood Squibb Pharmaceuticals, Inc. (WWS). Specifically, you request that the FDA' s standards for bioequivalence testing and approval of generic versions of ammonium lactate lotions require well-controlled clinical trials with (1) test measures that are well-validated (that is, that FDA exclude the use of the transepidermal water loss (TEWL) methodology in bioequivalence testing); (2) point-in-time (including regression) testing; and (3) testing for each separate disease indication (Petition at 1,4, 5, 7, 8, 9). For the reasons set forth below, your petition is granted in part and denied in part.

You state in your petition (Petition at 5) that you became aware that FDA recommended the following two methods for demonstrating bioequivalence of generic ammonium lactate lotion:

- a three-arm, vehicle-controlled, parallel group design bioequivalence study with clinical endpoints to show clinical efficacy in ichthyosis vulgaris and xerosis, or

- a three-arm, vehicle-controlled, parallel group design in ichthyosis vulgaris patients with a single clinical endpoint (scaling) and a surrogate clinical measure of TEWL.

Of these two methods, you assert that the first method is adequate in many regards to demonstrate bioequivalence and "only fails to incorporate point-in-time (including regression) testing" (Petition at 5). You object to the second method because it includes testing for only one of the reference listed drug's (RLD's) two labeled indications and uses only one clinical endpoint (Petition at 5). You also claim that the second method is deficient because it fails to include point-in-time testing and uses TEWL, which you assert is a poorly validated surrogate test methodology that has not demonstrated accuracy, sensitivity, and reproducibility (Petition at 5).

95P- 0379 CR 1

I. BACKGROUND

Since you submitted your petition, we have modified our advice on establishing bioequivalence of ammonium lactate lotions. FDA has amended its initial recommendation for an additional bioequivalence study as its thinking regarding the determination of equivalence for ammonium lactate lotions has evolved. As described above, one of the original recommendations for bioequivalence studies for ammonium lactate lotions was for a three-arm, vehicle-controlled, parallel group design bioequivalence study with clinical endpoints to show clinical efficacy in ichthyosis vulgaris and xerosis. This recommendation reflected the concern of the Division of Dermatological and Dental Products and the Office of Generic Drugs about the potential effect of differences in formulation between generic ammonium lactate lotions and the RLD in the treatment of the different conditions, ichthyosis vulgaris and xerosis. However, upon reconsideration of the issue following further internal discussions, they ultimately concluded that where the test and reference formulations are the same, a demonstration of bioequivalence in ichthyosis vulgaris will predict bioequivalence of the product in xerosis.

Presently, FDA recommends a single, three-arm, vehicle-controlled, randomized parallel group design bioequivalence study with clinical endpoints to show clinical efficacy in ichthyosis vulgaris. Ichthyosis vulgaris is more difficult to treat than xerosis. A demonstration of bioequivalence in the treatment of ichthyosis vulgaris will confer approval for the xerosis indication provided that the test and reference formulations are qualitatively and quantitatively the same. It is generally the current practice for locally acting drugs that have more than one related indication to demonstrate bioequivalence by conducting the bioequivalence study in a single indication, usually the one that is most difficult to treat. (See, e.g., Docket 88P-0369/CP&PSA, July 1, 1994, response to citizen petition submitted by Ms. Claudia Wolback, Janssen Research Foundation (recommending a single clinical study to determine bioequivalence for mebendazole-containing products); draft guidance on *Performance of a Bioequivalence Study for Topical Antifungal Products*, Feb. 24, 1990.)

II. WWS'S CONCERNS

A. Transepidermal Water Loss (TEWL) Methodology

Our current advice satisfies most of your concerns about appropriate bioequivalence testing for generic ammonium lactate lotions. We agree that, to date, the TEWL methodology has not been adequately validated as a surrogate marker of bioequivalence. Thus, we do not currently recommend the use of the TEWL method in bioequivalence testing of generic ammonium lactate lotions. Therefore, your request that FDA refrain at this time from recommending the TEWL method to assess bioequivalence of ammonium lactate lotions is granted.

B. Point-in-Time and Regression Testing

To demonstrate bioequivalence, we also recommend that the study design include a sufficient length of time to document treatment effect as well as reemergence of signs and symptoms of the disease condition on discontinuing therapy. Accordingly, your request that FDA recommend point-in-time and regression testing to establish bioequivalence for ammonium lactate lotions is granted.

C. Separate Clinical Trials for Each Labeled Disease Indication

You assert that a demonstration of bioequivalence of generic ammonium lactate lotion should include testing in each condition indicated on the drug's label (i.e., ichthyosis vulgaris and xerosis) because these conditions represent two distinct disease states and have distinct drug responses to chemical agents (Petition at 7). You claim that FDA has always treated ichthyosis and xerosis as separate diseases because FDA required testing in both diseases to support approval of LacHydrin lotion and LacHydrin cream, both subjects of new drug applications (NDAs) (Petition at 7).

1. *Statute and Regulations*

The Federal Food, Drug, and Cosmetic Act (the Act) requires a new drug applicant to demonstrate evidence of safety and effectiveness for each of the drug's labeled conditions of use (section 505 (b) and (d) (21 U.S.C. 355 (b) and (d)). The Act generally permits FDA, in evaluating abbreviated new drug applications (ANDAs), to rely on the finding of safety and effectiveness for the RLD approved in the NDA, in this case, the data showing that ammonium lactate lotion is effective in treating ichthyosis vulgaris and xerosis. (See section 505(j)(2) of the Act (21 U.S.C. 355(j)(2)).)

With respect to ANDAs, section 505(j)(2)(A)(iv) of the Act specifies that an ANDA must contain information to show that the proposed generic drug is bioequivalent to the listed drug to which it refers. Under section 505(j)(4)(F) of the Act, FDA may refuse to approve an ANDA if "information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application . . . ."

The data necessary to establish bioequivalence of a generic ammonium lactate lotion with the RLD differ from those necessary to establish the safety and effectiveness of the RLD in an NDA. Under 21 CFR 320.24(a) and (b)(4), FDA "may require in vivo or in vitro testing, or both, to establish . . . the bioequivalence of specific drug products," including ". . . appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence." Neither the statute nor the regulations require an applicant to submit comparative clinical trial data for each separate

disease indication before FDA may approve an ANDA. It is well-accepted that FDA has wide discretion to determine how the bioequivalence requirement is met; FDA's discretion need only be based on a " 'reasonable and scientifically supported criterion, whether [the agency] chooses to do so on a case-by-case basis or through more general inferences about a category of drugs . . . ' " (*Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 218 (D.D.C. 1996) (quoting *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 651 (D.D.C. 1992), *vacated as moot sub nom, Schering Corp. v. Shalala*, 995 F.2d 1103 (D.C. Cir. 1993))). Thus, a comparative clinical trial to establish bioequivalence with the RLD in each labeled indication is not required by the Act or its implementing regulations.

2. *Discussions*

As stated in section I above, based on our experience and scientific expertise, we recommend a single study with clinical endpoints to show clinical efficacy in ichthyosis vulgaris to assess bioequivalence of ammonium lactate lotion. Generally, bioequivalence testing for topical products using clinical studies with clinical endpoints relies on a single study in one indication, usually the one that is most difficult to treat. If the generic drug product is shown to be bioequivalent for one indication, it is expected to be bioequivalent for all related indications with the same site of action.

For example, in assessing bioequivalence for mebendazole-containing products (which are locally acting anthelminthics), FDA requires a bioequivalence study only in the roundworm indication. Although mebendazole-containing products are also indicated for pinworm, hookworm, and whipworm infestations, these indications are related to roundworm and also affect the gastrointestinal tract. FDA recommends a single bioequivalence study in the roundworm indication because it is more difficult to treat than pinworm.[1] (See Docket 88P-0369/CP&PSA, July 1, 1994, response to citizen petition submitted by Ms. Claudia Wolback, Janssen Research Foundation.)

Similarly, FDA's longstanding recommendation with respect to topical antifungal products has been to demonstrate bioequivalence using a single clinical study in patients with the tinea pedis indication. (See, e.g., draft guidance on *Performance of a Bioequivalence Study for Topical Antifungal Products*, Feb. 24, 1990.) This is true even though topical antifungal products are also indicated for tinea corporis and tinea cruris, because these indications are related to tinea pedis and also affect the skin.

In the case you present, ichthyosis vulgaris and xerosis are related indications that affect the skin, and the presumed mode of action of ammonium lactate lotion is similar for both indications. Thus, we have determined that it is unnecessary to require studies in both ichthyosis vulgaris and

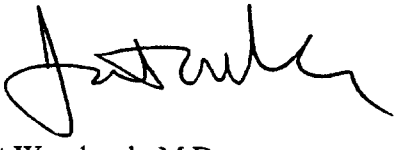
[1] The whipworm and hookworm indications were not considered to be reasonable endpoints for comparative clinical trials because these indications are relatively rare in the United States.

xerosis to demonstrate the bioequivalence of generic ammonium lactate lotion to the RLD. Therefore, your request that FDA require bioequivalence testing for both ichthyosis vulgaris and xerosis is denied.

III. CONCLUSION

To summarize, we grant your request that TEWL not be used in bioequivalence testing for ammonium lactate lotion at this time. We grant your request that point-in-time and regression testing be used to establish bioequivalence for ammonium lactate lotion. Finally, we deny your request to require that generic applicants of ammonium lactate lotion conduct bioequivalence studies in both ichthyosis vulgaris and xerosis. This response represents our current advice on establishing bioequivalence for generic ammonium lactate lotions.

Sincerely yours,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research